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(12) UK Patent Application (19) GB (11) 2 325 224 (13) A

(43) Date of A Publication 18.11.1998

(21) Application No 9807606.0

(22) Date of Filing 08.04.1998

(30) Priority Data
(31) 9709810 (32) 14.05.1997 (33) GB

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(51) INT CL^6
C07D 239/30

(52) UK CL (Edition P)
C2C CEJ C1600 C215 C247 C25Y C250 C252 C30X C31Y C313 C337 C440 C69Y

(56) Documents Cited
GB 2287466 A EP 0745593 A2 WO 96/23776 A1

(58) Field of Search
UK CL (Edition P) C2C CZL
INT CL^6 C07D 239/30
Online:CAS-ONLINE,WPI

(54) Abstract Title
Preparation of 4,6-dichloropyrimidine

(57) A process for obtaining 4,6-dichloropyrimidine comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride at 70-110°C to leave a reaction mixture; and

(a) adding water to the reaction mixture at 50-80°C to give a resulting mixture, and extracting 4,6-dichloropyrimidine from the resulting mixture with an extraction solvent at 30-100°C;
or

(b) either

(i) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:4, extracting 4,6-dichloropyrimidine from the reaction mixture with an extraction solvent at 30-100°C; or

(ii) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:10 or higher, removing excess phosphorus oxychloride by distillation to leave a residue, and extracting 4,6-dichloropyrimidine from the residue with an extraction solvent at 30-100°C.

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CHEMICAL PROCESS

The present invention concerns 4,6-dichloropyrimidine, an intermediate in the agrochemical industry.

Processes for preparing 4,6-dichloropyrimidines are reported in the literature (see, for example, GB2287466, EP-A1-0682018, EP-A1-0697406, EP-A1-0761653 and WO95/2166).

The present invention provides a process for obtaining 4,6-dichloropyrimidine comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride at a temperature in the range 70-110°C to leave a reaction mixture; and

(a) adding water to the reaction mixture at a temperature in the range 50-80°C to give a resulting mixture, and extracting 4,6-dichloropyrimidine from the resulting mixture with an extraction solvent at a temperature in the range 30-100°C;

or

(b) either

(i) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:4 (preferably 1:2 to 1:3.5), extracting 4,6-dichloropyrimidine from the reaction mixture with an extraction solvent at a temperature in the range 30-100°C; or

(ii) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:10 or higher, removing excess phosphorus oxychloride by distillation to leave a residue, and extracting 4,6-dichloropyrimidine from the residue with an extraction solvent at a temperature in the range 30-100°C.

The reaction of 4,6-dihydroxypyrimidine and phosphorus oxychloride may be carried out as a melt or in the presence of a solvent. When a solvent is used, the solvent is the same as the extraction solvent employed.

It is preferred that the molar ratio of 4,6-dihydroxypyrimidine: phosphorus oxychloride is in the range 1:2 to 1:10 (especially 1:2 to 1:7).

In step (a) above it is preferred that the amount of water added is, or is between:

- the amount required to just fully hydrolyse any chlorinated phosphorus compounds remaining after the reaction of 4,6-dihydroxypyrimidine and phosphorus oxychloride, and
- the amount required to partially hydrolyse the phosphorus oxychloride such that there is no phosphorus oxychloride remaining.

Thus, for example, if one mole of 4,6-dihydroxypyrimidine is reacted with five moles of phosphorus oxychloride, and if it is assumed that one mole of 4,6-dichloroxypyrimidine is produced, then it is preferred that the amount of water added is, or is between, 3 and 13 moles.

In step (b)(ii) it is preferred that the distillation is carried out under reduced pressure.

Suitable extraction solvents are solvents that are inert under the conditions used and that are poor solvents for phosphorus by-products produced during the reaction and should have a boiling point such that the solvent and the 4,6-dichloropyrimidine can be easily separated by distillation. Such solvents are unsaturated or saturated hydrocarbons (such as aromatic solvents (for example toluene or xylene), straight or branched chain hydrocarbons (for example pentane, hexane or heptane) or optionally alkyl substituted C_{5-7} cycloalkanes (for example cyclohexane, cyclopentane or methylcyclohexane)), ethers (for example methyl *tert*-butylether) or halogenated aromatics (such as halobenzenes (for example chlorobenzene or fluorobenzene)). Preferred extraction solvents are *n*-hexane, methylcyclohexane, toluene or cyclohexane. It is particularly preferred that the extraction solvent is methylcyclohexane.

It is preferred that the extraction of 4,6-dichloropyrimidine with an extraction solvent is carried out at a temperature in the range 50-80°C.

It is preferred that the extraction of 4,6-dichloropyrimidine with an extraction solvent is by an exhaustive extraction technique such as a multistage extraction (for example counter-current extraction).

When the phosphorus oxychloride reacts with 4,6-dihydroxypyrimidine phosphorus by-products are produced. These by-products can be converted back to phosphorus oxychloride by reacting them with phosphorus pentachloride or a mixture of phosphorus trichloride and chlorine. (See, for example, the disclosures in US3845194 and WO94/14774.)

In one aspect the present invention provides a process for obtaining 4,6-dichloropyrimidine comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride, optionally in the presence of a base or a salt of a base, at a temperature in the range 70-110°C to leave a reaction mixture; and

(a) adding water to the reaction mixture at a temperature in the range 50-80°C to give a resulting mixture, and extracting 4,6-dichloropyrimidine from the resulting mixture with

an extraction solvent at a temperature in the range 30-100°C;

or

(b) and when no base or salt of a base is used, either

(i) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:3.5, extracting 4,6-dichloropyrimidine from the reaction mixture with an extraction solvent at a temperature in the range 30-100°C; or

(ii)when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:10 or higher, removing excess phosphorus oxychloride by distillation to leave a residue, and extracting 4,6-dichloropyrimidine from the residue with an extraction solvent at a temperature in the range 30-100°C.

Suitable bases include secondary and tertiary amines, particularly amines of formula $R^1R^2R^3N$ wherein R^1, R^2 and R^3 are, independently, C_{1-10} alkyl (especially C_{1-6} alkyl) or C_{3-6} cycloalkyl or R^1 and R^2 join to form a piperidine or pyrrolidine ring, or R^3 may also be hydrogen. Saturated hindered amines include, for example, N,N-di*iso*propylethylamine (Hünig's base), triethylamine, N,N-di*iso*propylmethylamine, N,N-di*iso*propyl*iso*butylamine, N,N-di*iso*propyl-2-ethylbutylamine, N,N-dicyclohexylmethylamine, N,N-dicyclohexylethylamine, N-*tert*-butylcyclohexylamine, N-methylpyrrolidine or N-ethylpiperidine. Salts of bases include hydrochloride salts, especially hydrochloride salts of any of the foregoing bases.

In another aspect the present invention provides a process for obtaining 4,6-dichloropyrimidine comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride in the presence of a base or a salt of a base at a temperature in the range 70-110°C to leave a reaction mixture; adding water to the reaction mixture at a temperature in the range 50-80°C to give a resulting mixture; and extracting 4,6-dichloropyrimidine from the resulting mixture with an extraction solvent at a temperature in the range 30-100°C.

In yet another aspect the present invention provides a process for obtaining 4,6-dichloropyrimidine comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride in the absence of a base or a salt of a base at a temperature in the range 70-110°C to leave a reaction mixture; adding water to the reaction mixture at a temperature in the range 50-80°C to give a resulting mixture; and extracting 4,6-dichloropyrimidine from the resulting mixture with an extraction solvent at a temperature in the range 30-100°C.

In a further aspect the present invention provides a process for obtaining 4,6-dichloropyrimidine comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride, optionally in the presence of a base or a salt of a base, at a temperature in the range 80-90°C to leave a reaction mixture; and

(a) adding water to the reaction mixture at a temperature in the range 60-80°C to give a resulting mixture, the amount of water being, or being between, the amount required to just fully hydrolyse any chlorinated phosphorus compounds remaining after the reaction of 4,6-dihydroxypyrimidine and phosphorus oxychloride, and the amount required to partially hydrolyse the phosphorus oxychloride such that there is no phosphorus oxychloride remaining; and extracting 4,6-dichloropyrimidine from the resulting mixture with methylcyclohexane at a temperature in the range 50-80°C;

or

(b) and when no base or salt of a base is used, either

(i) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:3.5, extracting 4,6-dichloropyrimidine from the reaction mixture with methylcyclohexane at a temperature in the range 50-80°C; or

(ii) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:10 or higher, removing excess phosphorus oxychloride by distillation to leave a residue, and extracting 4,6-dichloropyrimidine from the residue with methylcyclohexane at a temperature in the range 50-80°C.

Examples 1, 3, 4, 5, 6, 7 and 8 illustrate the invention. Example 2 does not form part of the present invention. Throughout the Examples the abbreviation hplc means high pressure liquid chromatography.

EXAMPLE 1

4,6-Dihydroxypyrimidine (5g, 1 equivalent) and phosphorus oxychloride (15g, 2.2 equivalents) were stirred at 85-90°C for 2 hours. The reaction mixture was cooled to 60°C and methylcyclohexane added. The methylcyclohexane was separated and the reaction mixture extracted 6 times with methylcyclohexane (total 130ml of methylcyclohexane used). The methylcyclohexane extracts were combined and evaporated in vacuo to leave 4,6-dichloropyrimidine (3.0g, 99% pure by qualitative hplc; no phosphorus detected by ^{31}P NMR).

EXAMPLE 2

4,6-Dihydroxypyrimidine (20g, 1 equivalent) and phosphorus oxychloride (136.6g, 5 equivalents) were stirred at 90°C for 2 hours. The reaction mixture was cooled to 60°C and extracted with methylcyclohexane (3 x 150ml) at 60-70°C. The methylcyclohexane extracts were combined and evaporated in vacuo to leave 4,6-dichloropyrimidine as an orange, waxy solid. The solid was dried in a dessicator and yielded 4,6-dichloropyrimidine (15.2g, 57.9% pure by quantitative hplc).

EXAMPLE 3

4,6-Dihydroxypyrimidine (20g, 1 equivalent) and phosphorus oxychloride (136.3g, 5 equivalents) were stirred at 90°C for 2 hours. The reaction mixture was cooled and excess phosphorus oxychloride removed by distillation (pressure 180-150mm Hg; temperature of reaction mixture 66-70°C; head temperature 46°C) to leave a residue. The residue was extracted at 60-70°C with methylcyclohexane (3 x 150ml). The extracts were combined and evaporated in vacuo to leave 4,6-dichloropyrimidine as a crystalline material. The material was dried in a dessicator and yielded 4,6-dichloropyrimidine (11.15g; 98.7% pure by qualitative hplc; only a trace of phosphorus detected by ^{31}P NMR).

EXAMPLE 4

4,6-Dihydroxypyrimidine (20g, 1 equivalent) and phosphorus oxychloride (136.6g, 5 equivalents) were stirred at 90°C for 2 hours. The reaction mixture was cooled to 60°C and methylcyclohexane (150ml) and water (42ml, 13 equivalents; slow addition) were added sequentially maintaining the temperature in the range 60-70°C. The resulting mixture was stirred for 1 hour at 60-70°C, the organic layer separated and the aqueous extracted with methylcyclohexane (2 x 150ml). The organic extracts were combined and evaporated in vacuo to leave 4,6-dichloropyrimidine as a white crystalline material (0.2g, 99.8% pure by qualitative hplc; no phosphorus detected by ^{31}P NMR).

EXAMPLE 5

4,6-Dihydroxypyrimidine (20g, 1 equivalent) and phosphorus oxychloride (136.6g, 5 equivalents) were stirred at 90°C for 2 hours. The reaction mixture was cooled to 60°C and methylcyclohexane (150ml) and water (9.6ml, 3 equivalents; slow addition) were added sequentially maintaining the temperature in the range 60-70°C. The resulting mixture was stirred for 1 hour at 60-70°C, the organic layer separated and the aqueous extracted with methylcyclohexane (2 x 150ml). The organic extracts were combined and evaporated in

vacuo to leave 4,6-dichloropyrimidine (4.6g, 96.4% pure by qualitative hplc; no phosphorus detected by ^{31}P NMR).

EXAMPLE 6

4,6-Dihydroxypyrimidine (20g, 1 equivalent) and phosphorus oxychloride (60.2g, 2.2 equivalents) were stirred at 90°C for 2 hours. The reaction mixture was cooled to 60°C and methylcyclohexane (150ml) added. The methylcyclohexane was separated and the reaction mixture extracted with further amounts of methylcyclohexane (2x150ml). The methylcyclohexane extracts were combined and evaporated in vacuo to leave 4,6-dichloropyrimidine as a white solid (6.4g, 99.1% pure by qualitative hplc, 97.02% pure by quantitative hplc).

EXAMPLE 7

4,6-Dihydroxypyrimidine (20g, 1 equivalent) and phosphorus oxychloride (82.1g, 3 equivalents) were stirred at 90°C for 2 hours. The reaction mixture was cooled to 60°C, methylcyclohexane (100ml) added and this was stirred at 60°C for 1 hour. The methylcyclohexane was separated and the reaction mixture extracted with further amounts of methylcyclohexane (3x100ml). The methylcyclohexane extracts were combined and evaporated in vacuo to leave 4,6-dichloropyrimidine as yellow crystals (8.5g, 99.7% pure by qualitative hplc, 92.75% pure by quantitative hplc).

EXAMPLE 8

4,6-Dihydroxypyrimidine (20g, 1 equivalent) and phosphorus oxychloride (82.1g, 3 equivalents) were stirred at 90°C for 2 hours. The reaction mixture was cooled and excess phosphorus oxychloride removed by distillation (pressure 150mm Hg, temperature 65-70°C) to leave a residue. The residue was extracted at 60-70°C with methylcyclohexane (4 x 100ml). The extracts were combined and evaporated in vacuo to leave 4,6-dichloropyrimidine as a crystalline material (6.9g; 99.5% pure by qualitative hplc, 93.2% pure by quantitative hplc).

CLAIMS

1. A process for obtaining 4,6-dichloropyrimidine comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride at a temperature in the range 70-110°C to leave a reaction mixture; and

(a) adding water to the reaction mixture at a temperature in the range 50-80°C to give a resulting mixture, and extracting 4,6-dichloropyrimidine from the resulting mixture with an extraction solvent at a temperature in the range 30-100°C;

or

(b) either

(i) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:4, extracting 4,6-dichloropyrimidine from the reaction mixture with an extraction solvent at a temperature in the range 30-100°C; or

(ii) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:10 or higher, removing excess phosphorus oxychloride by distillation to leave a residue, and extracting 4,6-dichloropyrimidine from the residue with an extraction solvent at a temperature in the range 30-100°C.

2. A process according to claim 1 comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride, optionally in the presence of a base or a salt of a base, at a temperature in the range 70-110°C to leave a reaction mixture; and

(a) adding water to the reaction mixture at a temperature in the range 50-80°C to give a resulting mixture, and extracting 4,6-dichloropyrimidine from the resulting mixture with an extraction solvent at a temperature in the range 30-100°C;

or

(b) and when no base or salt of a base is used, either

(i) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:3.5, extracting 4,6-dichloropyrimidine from the reaction mixture with an extraction solvent at a temperature in the range 30-100°C; or

(ii) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:10 or higher, removing excess phosphorus oxychloride by distillation to leave a residue, and extracting 4,6-dichloropyrimidine from the residue with an extraction solvent at a temperature in the range 30-100°C.

3. A process according to claim 1 comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride in the presence of a base or a salt of a base at a temperature in the range 70-110°C to leave a reaction mixture; adding water to the reaction mixture at a temperature in the range 50-80°C to give a resulting mixture; and extracting 4,6-dichloropyrimidine from the resulting mixture with an extraction solvent at a temperature in the range 30-100°C.

4. A process according to claim 1 comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride in the absence of a base or a salt of a base at a temperature in the range 70-110°C to leave a reaction mixture; adding water to the reaction mixture at a temperature in the range 50-80°C to give a resulting mixture; and extracting 4,6-dichloropyrimidine from the resulting mixture with an extraction solvent at a temperature in the range 30-100°C.

5. A process according to claim 1 comprising comprising reacting 4,6-dihydroxypyrimidine with phosphorus oxychloride, optionally in the presence of a base or a salt of a base, at a temperature in the range 80-90°C to leave a reaction mixture; and

(a) adding water to the reaction mixture at a temperature in the range 60-80°C to give a resulting mixture, the amount of water being, or being between, the amount required to just fully hydrolyse any chlorinated phosphorus compounds remaining after the reaction of 4,6-dihydroxypyrimidine and phosphorus oxychloride, and the amount required to partially hydrolyse the phosphorus oxychloride such that there is no phosphorus oxychloride remaining; and extracting 4,6-dichloropyrimidine from the resulting mixture with methylcyclohexane at a temperature in the range 50-80°C;

<u>or</u>

(b) and when no base or salt of a base is used, either

(i) when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:3.5, extracting 4,6-dichloropyrimidine from the reaction mixture with methylcyclohexane at a temperature in the range 50-80°C; or

(i)when the molar ratio of 4,6-dihydroxypyrimidine:phosphorus oxychloride is in the range 1:2 to 1:10 or higher, removing excess phosphorus oxychloride by distillation to leave a residue, and extracting 4,6-dichloropyrimidine from the residue with methylcyclohexane at a temperature in the range 50-80°C.

6. A process according to claim 1 substantially as described in any one of Examples 1, 3, 4, 5, 6, 7 or 8.

7. 4,6-Dichloropyrimidine whenever made by a process claimed in any one of claims 1 to 6.

The Patent Office

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Application N : GB 9807606.0
Claims searched: 1-7

Examiner: Anwar Gilani
Date of search: 17 July 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): C2C (CZL)

Int Cl (Ed.6): C07D-239/30

Other: Online:CAS-ONLINE, WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
Y	GB2287466 A	(HÜLS) example 2	1-5,7
X Y	EP0745593 A2	(DSM CHEMIE LINZ) example 1, particularly col.3 l.39-41	1-5,7 1-5,7
X Y	WO96/23776 A1	(ZENECA) examples	1-5,7 1-5,7

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
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